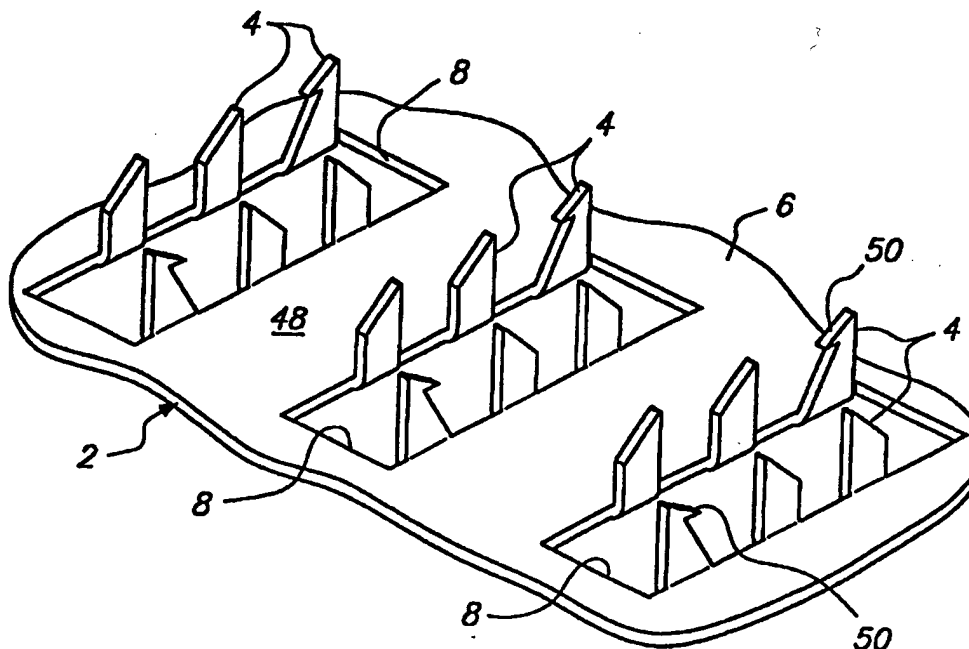




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61N 1/30	A1	(11) International Publication Number: WO 97/48440 (43) International Publication Date: 24 December 1997 (24.12.97)
<p>(21) International Application Number: PCT/US97/10516</p> <p>(22) International Filing Date: 17 June 1997 (17.06.97)</p> <p>(30) Priority Data: 60/019,990 18 June 1996 (18.06.96) US</p> <p>(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p> <p>(72) Inventors: CORMIER, Michel, J., N.; 278 Andsbury Avenue, Mountain View, CA 94043 (US). NEUKERMANS, Armand, P.; 3510 Arbutus Avenue, Palo Alto, CA 94303 (US). BLOCK, Barry; 30610 Page Mill Road, Los Altos, CA 94022 (US). THEEUWES, Felix, T.; 27350 Altamont Road, Los Altos, CA 94022 (US). AMKRAUT, Alfred, A.; 3358 Kenneth Drive, Palo Alto, CA 94303 (US).</p> <p>(74) Agents: MILLER, D., Byron et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: DEVICE FOR ENHANCING TRANSDERMAL AGENT DELIVERY OR SAMPLING



(57) Abstract

A percutaneous agent delivery or sampling device (10, 88, 98, 104) comprising a sheet (6) having a plurality of microblades (4) for piercing and anchoring to the skin for increasing transdermal flux of an agent and for improving the attachment of the device (10, 88, 98, 104) to the skin. The device comprises a sheet (6) having at least one opening (8) therethrough and a plurality of blades (4) extending downward therefrom, and an anchoring means for anchoring the device (2) to the body surface.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LJ	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

**DEVICE FOR ENHANCING TRANSDERMAL AGENT
DELIVERY OR SAMPLING**

Field of the Invention

The present invention relates to transdermal agent delivery and sampling. More particularly, this invention relates to the transdermal delivery of agents, such as peptides and proteins, as well as the transdermal sampling of agents, such as glucose, body electrolytes and substances of abuse, such as but not limited to alcohol and illicit drugs. The present invention uses skin-piercing microblades to enhance the transdermal flux of the agents during transdermal delivery or sampling and anchoring elements to assist in retaining the delivery or sampling device in the skin.

Background of the Invention

Interest in the percutaneous or transdermal delivery of peptides and proteins to the human body continues to grow with the increasing number of medically useful peptides and proteins becoming available in large quantities and pure form. The transdermal delivery of peptides and proteins still faces significant problems. In many instances, the rate of delivery or flux of polypeptides through the skin is insufficient to produce a desired therapeutic effect due to the binding of the polypeptides to the skin. In addition, polypeptides and proteins are easily degraded during and after penetration into the skin, prior to reaching target cells. Likewise, the passive flux of water soluble small molecules such as salts is limited.

One method of increasing the transdermal delivery of agents relies on the application of an electric current across the body surface or on "electrotransport". "Electrotransport" refers generally to the passage of a beneficial agent, e.g., a drug or drug precursor, through a body surface such as skin, mucous membranes, nails, and the like. The transport of the agent is induced or enhanced by the application of an electrical potential, which results in the application of electric current, which delivers or enhances delivery of the agent. The electrotransport of agents through a body surface

1 may be attained in various manners. One widely used electrotransport process,
2 iontophoresis, involves the electrically induced transport of charged ions.
3 Electroosmosis, another type of electrotransport process, involves the movement of a
4 solvent with the agent through a membrane under the influence of an electric field.
5 Electroporation, still another type of electrotransport, involves the passage of an agent
6 through pores formed by applying a high voltage electrical pulse to a membrane. In
7 many instances, more than one of these processes may be occurring simultaneously to
8 different extents. Electrotransport delivery generally increases agent delivery,
9 particularly large molecular weight species (e.g., polypeptides) delivery rates, relative
10 to passive or non-electrically assisted transdermal delivery. However, further increases
11 in transdermal delivery rates and reductions in polypeptide degradation during
12 transdermal delivery are highly desirable.

13 One method of increasing the agent transdermal delivery rate involves pre-
14 treating the skin with, or alternatively co-delivering with the beneficial agent, a skin
15 permeation enhancer. The term "permeation enhancer" is broadly used herein to
16 describe a substance which, when applied to a body surface through which the agent is
17 delivered, enhances its electrotransport flux. The mechanism may involve a reduction
18 of the electrical resistance of the body surface to the passage of the agent
19 therethrough, an increase in the permeability of the body surface, the creation of
20 hydrophilic pathways through the body surface, and/or a reduction in the degradation of
21 the agent (e.g., degradation by skin enzymes) during electrotransport.

22 There have been many attempts to enhance transdermal flux by mechanically
23 puncturing the skin prior to transdermal drug delivery. See for example U.S. Patent
24 Nos. 5,279,544 issued to Gross et al., 5,250,023 issued to Lee et al., and 3,964,482
25 issued to Gerstel et al. These devices utilize tubular or cylindrical structures generally,
26 although Gerstel does disclose the use of other shapes, to pierce the outer layer of the
27 skin. Each of these devices provide manufacturing challenges, limited mechanical
28 attachment of the structure to the skin, and/or undesirable irritation of the skin.

1 As has been discussed, a variety of chemicals and mechanical means have
2 been explored to enhance transdermal flux. However, there is still a need to provide a
3 device suitable for increasing transdermal flux which device is low-cost and which can
4 be manufactured reproducibly (i.e., without significant variation from device to device)
5 in high volume production and to improve the attachment of the device to the skin.

6

7

Description of the Invention

8

9 The present invention provides a reproducible, high volume production, low-cost
10 device suitable for increasing transdermal flux and improving attachment to the skin
11 with minimal to no skin irritation. The device generally comprises a structure that
12 attaches to the skin more effectively than the prior art devices. The invention
13 comprises a plurality of microblades for piercing and anchoring to the skin. The blades
14 typically have a length of less than about 0.4 mm and a width and thickness which is
15 even smaller. In spite of their small size, the blades can be made with an extremely
16 reproducible size and shape so that the microslits formed by the blades puncturing the
17 skin also have a very reproducible size and depth. Because the blades have a small
18 thickness (i.e., small relative to the width and length of the blades), the blades produce
19 less tissue damage for a given cross-section than a skin piercing microneedle having a
20 circular cross-section. The device of the present invention pierces the stratum
21 comeum of a body surface to form pathways through which a substance (e.g., a drug)
22 can be introduced (i.e., delivery) or through which a substance (e.g., a body electrolyte)
23 can be withdrawn (i.e., sampling).

24 In one aspect of the invention, the device comprises a sheet having a plurality of
25 openings therethrough, a plurality of microblades integral therewith and extending
26 downward therefrom, and means for anchoring the device to a body surface. In the
27 many different aspects of the invention, the device is anchored to the body surface in
28 any of plurality of ways, including but not limited to, having an extension such as a
29 prong or barb extending from at least some of the microblades, having an opening
30 extending perpendicular through at least some of the microblades, covering essentially
31 the entire surface area of the skin contacting surface of the device with adhesive except

1 for one side of the microblades, orienting at least some of the plurality of microblades at
2 an angle of 90° to the remainder of the plurality of microblades, orienting at least some
3 of the plurality of microblades at an angle within a range of about 1° to about 89° with
4 respect to the remainder of the plurality of microblades, providing a plurality of second
5 openings through the sheet which make the device more shapeable with respect to the
6 body surface. The device of the present invention can be used in connection with drug
7 delivery, body analyte or drug sampling, or both. Delivery devices for use with the
8 present invention include, but are not limited to, electrotransport devices, passive
9 devices, osmotic devices and pressure-driven devices. Sampling devices for use with
10 the present invention include, but are not limited to, "reverse" electrotransport devices
11 as disclosed in Glikfeld et al., U.S. Patent No. 5,279,543, passive devices, osmotic
12 devices and negative pressure driven devices.

13 The present invention also provides a high yield, low-cost method for producing,
14 in extremely reproducible fashion, the device of the present invention.

15

16 **Brief Description of the Drawings**

17

18 Figure 1 is a perspective exploded view of one embodiment of an
19 electrotransport agent delivery system with a blade array device according to one
20 embodiment of the present invention;

21 Figure 2 is an enlarged perspective view of the skin proximal side of the blade
22 array device in accordance with one embodiment of the present invention;

23 Figure 3 is a partial top plan view of a blade array pattern in accordance with
24 one embodiment of the present invention for forming blades with anchoring elements;

25 Figure 4 is partial top plan view of yet another embodiment of the blade array
26 pattern of Figure 3;

27 Figure 5 is an enlarged view of a portion of the blades of the blade array pattern
28 of Figure 3;

29 Figure 6 is an enlarged view of a blade tip in accordance with one embodiment
30 of the present invention;

1 Figure 7 is an enlarged view of a blade tip in accordance with another
2 embodiment of the present invention;

3 Figure 8 is a diagrammatic representation of a method for producing blades of
4 the present invention from the blade array pattern of figure 3;

5 Figure 9 is an enlarged cross-sectional view of angled blades in accordance
6 with one embodiment of the present invention;

7 Figures 10, 11 and 12 are yet other embodiments of the blades with anchoring
8 elements of the present invention;

9 Figure 13 is a right side elevational view of another embodiment of a blade with
10 an anchoring element;

11 Figure 14 is an end view of the blade of figure 13;

12 Figures 15 and 16 are another embodiment of the blade and an anchoring
13 element;

14 Figure 17 is a right side elevational view of a blade with anchoring elements in
15 accordance with one embodiment of the present invention;

16 Figure 18 is a cross-sectional view taken along line 18-18 of figure 17;

17 Figure 19 is a right side elevational view of another embodiment of a blade with
18 an anchoring element;

19 Figure 20 is an enlarged partial top plan view of still another embodiment of th
20 blade array pattern;

21 Figure 21 is an enlarged partial top plan view of yet another embodiment of the
22 blade array pattern;

23 Figure 22 is a bottom plan view of the electrotransport agent delivery system of
24 figure 1;

25 Figure 23 is a right side elevational view of the electrotransport agent delivery
26 system of figure 1;

27 Figure 24 is a rear elevational view of the electrotransport agent delivery system
28 of figure 1;

29 Figure 25 is a cross-sectional view taken along line 25-25 of the assembled
30 electrotransport agent delivery system of figure 23;

1 Figure 26 is a diagrammatic cross-sectional view of a passive agent delivery
2 system in accordance with one embodiment of the present invention;

3 Figure 27 is a diagrammatic cross-sectional view of another embodiment of a
4 passive agent delivery system in accordance with the present invention;

5 Figure 28 is a diagrammatic cross-sectional view of a sampling system in
6 accordance with one embodiment of the present invention; and

7 Figure 29 is a diagrammatic cross-sectional view of another embodiment of the
8 blades of the present invention.

9

10 **Modes for Carrying Out the Invention**

11

12 Turning now to the drawings in detail, one embodiment of the device 2 of the
13 present invention is generally shown in Figure 1 for use with electrotransport delivery
14 device 10. Device 2 is used for the percutaneous administration or sampling of an
15 agent. The terms "substance", "agent" and "drug" are used interchangeably herein and
16 broadly include physiologically or pharmacologically active substances for producing a
17 localized or systemic effect or effects in mammals including humans and primates,
18 avians, valuable domestic household, sport or farm animals, or for administering to
19 laboratory animals such as mice, rats, guinea pigs, and the like. These terms also
20 include substances such as glucose, electrolyte, alcohol, illicit drugs, etc. that can be
21 sampled through the skin. The major barrier properties of the skin, such as resistance
22 to drug penetration, reside with the stratum comeum. The inner division of the
23 epidermis generally comprises three layers commonly identified as stratum
24 granulosum, stratum malpighii, and stratum germinativum. Once a drug penetrates
25 below the stratum comeum, there is substantially less resistance to permeation through
26 the underlying stratum granulosum, stratum malpighii, and stratum germinativum layers
27 for absorption and circulation of drug into the body. The device of the present invention
28 is used to form microslits in the stratum comeum and produce a percolation area in the
29 skin for improved transdermal delivery or sampling of an agent.

1 D vice 2 comprises a plurality of microblades 4 (i.e., a blade array) extending
2 downward from one surface of a sheet or plate 6 (see Figure 2 in which device 2 is in
3 an inverted position to show the microblades). The microblades 4 penetrate the
4 stratum corneum of the epidermis when pressure is applied to the device to increase
5 the administration of or sampling of a substance through a body surface. The term
6 "body surface" as used herein refers generally to the skin, mucous membranes, and
7 nails of an animal or human, and to the outer surface of a plant.

8 Furthermore, the device 2 of the present invention improves the attachment of
9 the device to the skin so that the percolation areas and a continuous pathway are
10 preserved during movement of the body surface. In the embodiment shown in Figure
11 2, projections in the form of barbs 50 on at least one of the blades 4 assist in anchoring
12 the device 2 and any corresponding device or structure used in combination therewith
13 to the skin. Barbs 50 can be on any number of the blades from one blade to all blades.
14 Other embodiments which assist to anchor the device to the skin will be discussed
15 below.

16 The microblades 4 are generally formed from a single piece of material and are
17 sufficiently sharp and long for puncturing the stratum corneum of the skin. In one
18 embodiment, the microblades 4 and the sheet 6 are essentially impermeable or are
19 impermeable to the passage of an agent. The sheet 6 is formed with an opening 8
20 between the microblades 4 for enhancing the movement of an agent therethrough. In
21 the case of therapeutic agent (e.g., drug) delivery, the drug is released from a
22 drug-containing reservoir (not shown in Figure 2) through microslits formed by the
23 microblades 4 cutting through the stratum corneum, migrating down the outer surfaces
24 of the microblades and through the stratum corneum to achieve local or systemic
25 therapy. In the case of agent (e.g., body analyte) sampling, the analyte migrates from
26 the body through the microslits in the stratum corneum which are cut by the
27 microblades 4. In one embodiment, the opening 8 corresponds to the portion of the
28 sheet 6 occupied by each of the microblades 4 prior to the blades being
29 transpositioned into the downward depending position. The number of microblades 4
30 per opening can be any number, preferably however between 1 and about 30 blades
31 per opening. Furthermore, the number of openings per device and the number of

1 blades per device are independent. The device may have only one opening and one
2 microblade. The agent can be administered at a controlled rate of release from the
3 reservoir through an agent release rate controlling material (not shown) covering the
4 openings 8.

5 As is best shown in Figure 2, the microblades 4 have a thickness which is much
6 smaller than the width of the blades near their base, i.e., near the point where the
7 blades are attached to the plate 6. This blade geometry provides maximum drug
8 percolation area with a minimum blade penetration area, and hence less tissue
9 damage. The drug percolation area is the skin area in contact with the blades which
10 provides for drug penetration in the skin. The microblades are shaped with the largest
11 possible surface area with a minimal cross-sectional area so as to give the largest
12 possible percolation area. Thin microblades are better than round protrusions for this
13 purpose because for the same cross-section, a thin microblade produces more
14 percolation area and less tissue damage than a round protrusion. This is a crucial
15 advantage over the prior art round elements such as needles and tubes. Thin
16 microblades also require less insertion force than round protrusions. The width of each
17 blade can be any of a range of widths. The widths can be different from blade to blade
18 in the array pattern. Likewise, the width can be variable along the length of the blade,
19 as will be described in more detail below. The width of the blade at the intersection of
20 the blade and the body surface after the blade array has been inserted is preferably in
21 the range of about 25 μm to about 500 μm , more preferably about 50 μm to about 400
22 μm , more preferably 100 μm to about 300 μm .

23 In one embodiment, the microblades 4 (Figure 5) are also provided with slanted
24 (i.e., angled) leading edges 64 to further reduce the insertion force required to press
25 the microblades into the skin tissue. The angle of the leading edge is designated as α .
26 The slanted leading edges produce a cut through the skin tissue that is equal to the full
27 width of the blade 4 while reducing the amount of metal that is in the skin tissue. In
28 other words, a fiat leading edge (i.e., α is 90°) produces a blade with a larger amount of
29 blade material in the skin tissue than is produced by a blade having a slanted leading
30 edge. The leading edges of each blade can all be the same angle or can be at
31 different angles as shown in Figure 5. The angle α of each leading edge can be any

1 angle between about 10° to 90°, preferably between about 10° to 60°, more preferably
2 about 10° to 40°. The leading edge can also be segmented into two sections at
3 different angles. For example, the first segment can have an angle α between about
4 10° to 40° and then transition to a second segment having an angle between 20° to
5 60°. Alternatively, the leading edge of each blade can be arcuate (i.e., curved) in
6 shape, having, for example, a convex or concave shape. In one embodiment, the
7 leading edge is a curved tip across the entire width of the blade.

8 The microblades 4 are formed using a photo-etching process which is described
9 in detail hereinafter. This process allows the microblades 4 to be reproducibly formed
10 on a very small (i.e., tens of microns) scale. This process also allows the microblades
11 4 to be formed in shapes which help anchor device 2 to the skin. In one embodiment,
12 the microblades 4 are provided with barbs 50 (Figures 2, 3 and 5) in some fashion so
13 that the device 2 and any corresponding device attached thereto stays attached to the
14 skin after being applied with pressure. The degree of attachment and the number and
15 size of the barbs is such as to retain the delivery or sampling device during the normal
16 activity of the wearer, but not cause pain upon removal. As the microblades are
17 pressed into the skin tissue for use, the leading edge 64 of each microblade cuts
18 through and pushes aside the skin tissue. After the microblades have come to rest in
19 the skin, the skin due to its elastic nature at least partially comes back together around
20 the edges of the microblades, in this way the surface 66 on each microblade having a
21 barb 50 engages skin tissue and anchors the device in the skin. If the blade is left in
22 the skin for an extended period of time (e.g., 24 hours), the skin tissue begins to heal
23 together in the area behind the surface 66 of the barb thus improving the anchoring of
24 the device. Only one barb per blade is shown in the figures but it is within the scope of
25 the present invention that each blade can have a plurality of barbs extending therefrom.
26 The microblades, in one embodiment, have a cross-section that is wider in the area of
27 the skin distal end of the blade than in the area of the skin proximal end, thus providing
28 additional anchoring of the distal end in the skin. For example, the blades can have an
29 "arrowhead" shape. Furthermore, the barbs 50 shown in the figures are in the same
30 plane as the blade, however the barbs can be oriented outside of that plane for
31 example by a separate bending step or by using a shaped punch and die to produce a

1 curve in the blade and barb. Curving the tips of the blade outside the plane of the
2 blade generally provides better anchoring. Insertion of such blades causes the barbs
3 to curve in the curve direction but retraction causes them to return to their prior position.
4 The resulting curved cross-section of the blade can be, but is not limited to, angular,
5 semi-circular, C-shaped, or banana-shaped, to effect a larger cross-section of openings
6 in the skin.

7 The plurality of blades 4 for puncturing the stratum corneum are present on one
8 face surface 48 of the device 2 in any predetermined arrangement, for example, as a
9 cluster of blades spaced in rows having any desired number, or in any spaced apart
10 relation of one blade to each other. The device 2 of the embodiment shown in Figures
11 1 and 2 is produced by the pattern shown in Figure 3. Each blade has a width and
12 thickness that facilitates penetration of the stratum corneum without bending. In the
13 embodiment of Figure 3, there are six blades 4 in each opening 8 in sheet 6. Each
14 opening 8 in this embodiment is 1 mm long and 300 μm wide. Correspondingly, the
15 width of each blade is between about 137.5 μm to about 175 μm and the length is
16 about 250 μm . The required length of the blades is subject to variation of the body
17 surface being penetrated and corresponds to the natural thickness of the stratum
18 corneum, for one of the principle features of the invention is that the blades are to
19 penetrate the stratum corneum into the epidermis. Usually, the blades will be about 25
20 μm to about 400 μm in length, with the length for most applications being between
21 about 50 μm to about 200 μm .

22 The pattern for any of the blade array devices of the present invention are
23 produced with a photo-etching process. A thin sheet or plate 6 of metal such as
24 stainless steel or titanium is etched photo-lithographically with patterns containing
25 blade-like structures. In general, a thin laminate dry resist or wet resist is applied on a
26 sheet about 7 μm to about 100 μm thick, preferably about 25 μm to about 50 μm thick.
27 The resist is contact exposed using a mask having the desired pattern and is
28 subsequently developed. These operations are conducted in much the same way that
29 they are for the manufacture of a printed circuit board. The sheet is then etched using
30 acidic solutions. After the pattern has been etched through the sheet, the sheet is
31 placed on a die 52 (shown schematically in figure 8) having a plurality of openings 56

1 corresponding to the openings 8 in the sheet. A punch 54 having a plurality of
2 protrusions 58 corresponding to the openings in the sheet and die is initially located
3 above the sheet and die. At the initial stage, the blades 4 are in the same plane as the
4 rest of the sheet 6. The protrusions 58 on the punch 54 are then pressed into the
5 openings 56, thus bending the blades 4 downward to be at an angle (e.g., substantially
6 perpendicular) to the plane of the sheet. The finished structure provides blades 4 with
7 an adjacent opening 8 for the passage of a substance therethrough when the device 2
8 is applied to the skin. Rectangular openings 8 are shown in the figures but the
9 invention encompasses the use of any shape openings including, but not limited to,
10 square, triangular, circular and elliptical.

11 The sheet 6 in some areas can have additional etched openings 80 (Figure 4) to
12 alleviate the curl created during punching and/or to provide for flexibility in the dense
13 blade array patterns because in some embodiments the sheet becomes very stiff after
14 punching. The openings can be any of a variety of shapes (e.g., rectangular, circular,
15 elliptical, triangular, etc.) The openings also allow the sheet to be more easily curved to
16 match the curvature of the body surface to which it is to be attached which improves
17 anchoring of the device. The present invention maximizes the openings through the
18 sheet but with a sufficient number of horizontal and vertical continuous portions in the
19 sheet to prevent the sheet from being too flexible (i.e., flimsy). If the openings are
20 made too long in any one dimension, the sheet will bend (i.e., crinkle). In addition, it is
21 also possible to treat the devices after punching with heat or plastic deformation such
22 that the radius of curvature of the sheet becomes equal to or somewhat smaller than
23 the curvature of the body, where it is to be attached to enhance anchoring. The
24 concave surface can be shaped to match the convex pattern of the body.

25 The blades 4 can be patterned with resist on both sides 48,49 and subsequently
26 etched simultaneously from both sides (Figure 7) to achieve maximum pattern
27 resolution for a given sheet thickness and to produce a knife-like edge that can not be
28 achieved with conventional stamping and punching processes. Alternatively, the
29 blades 4 can be patterned and etched from one side (i.e., side 49) only (Figure 6).
30 When etching from one side only, the etching process can be controlled to etch
31 selective depths in the plate 6 along the length of the blades (e.g., at the blade tips) to

1 produce a single angle 60 at the tip of the blade which maximizes the sharpness of the
2 knife-like edge of the blade. In this embodiment, the lithography process produces a
3 portion of the blade that is thinner than the remainder of the thickness of the blade and
4 of the sheet. The lithography process also can produce very small dimensioned
5 elements for the anchoring and the penetration aspects of the invention.

6 In another embodiment of the two-sided etching process, the blade array pattern
7 of any of the embodiments of the present invention is etched into the top surface 49 of
8 sheet 6. A second pattern equivalent to the area bounded by each of the openings 8
9 (e.g., rectangular) is etched into the bottom surface 48 such that each of the blades in
10 the blade array pattern is thinner than the surrounding sheet 6. As a result, the sheet 6
11 forms a strong base and as the punch 54 deforms the blades 4 downward, each of the
12 blades plastically deforms so as to produce blades that are straighter and more truly
13 perpendicular to the sheet.

14 In one embodiment of the etching process, a dry resist (e.g., "Dynachem FL"
15 available from Dynachem located in Tustin, CA) is applied 12.5 μm thick to one or both
16 sides of the sheet and exposed in a standard manner. Then a suitable spray etcher
17 (e.g., "Dynamil VRP 1 Q/NM" available from Western Tech. Assoc. located in Anaheim,
18 CA) is used to spray a mixture of ferric chloride and hydrochloric acid onto the resist
19 and sheet at 52 °C (125 °F) for two minutes. A standard caustic stripper is used for the
20 resist removal.

21 In another embodiment of the etching process, a wet resist (e.g., "Shipley 111S"
22 available from Shipley Corporation, located in Marlborough, MA) is applied 7.5 μm thick
23 at about 20 °C (70 °F) to one or both sides of the sheet and exposed in a standard
24 manner. Then a suitable etchant (e.g., ferric chloride) is sprayed onto the resist and
25 sheet at 49 °C (120 °F). A standard caustic stripper is used for the resist removal.

26 Generally, the blades 4 are at an angle of about 90° to the surface 48 of the
27 sheet 6 after being punched, but they can be disposed at any angle forward or
28 backward from the perpendicular position that will facilitate penetration of and
29 attachment to the stratum comeum. In one embodiment (Figure 9), the blades are all
30 aligned at an angle between about 1° and about 89° degrees, preferably about 10° to
31 about 60°, more preferably about 20° to 45° to facilitate the device being slid along and

1 into the skin. The angled blades have two principal advantages. First, penetration of
2 the blades is not opposed by the elasticity of the skin because the blades are slid
3 horizontally into the skin as opposed to pressing vertically on the skin. Second, the
4 angled blades act to anchor the device in the skin as any motion of the skin is less
5 likely to dislodge the blades. In addition, other anchoring elements such as barbs,
6 openings, etc. can be used with the angled blades to further enhance anchoring of the
7 device.

8 In one embodiment (Figure 29), anchoring of the device is achieved by coating
9 the surface 48 of sheet 6 and surface 82 of each blade 4 with an adhesive. One
10 method of producing this embodiment comprises spraying the adhesive on the device 2
11 along the direction indicated by arrows 84. In this embodiment, the agent is free to
12 pass through the openings 8 and along surface 86 of each blade unencumbered by the
13 adhesive. It is also possible to apply the adhesive on only surface 48 and not on the
14 blade surfaces 82. This can be accomplished, for example, by applying the adhesive
15 onto surface 48 after the blades 82 have been punched by spraying the adhesive in a
16 direction which is parallel to the axis of the blades 82. It is further possible to apply the
17 adhesive only on the blade surfaces 82 and not on the surface 48 of sheet 6 in order to
18 anchor the device, although this last design is the least preferred adhesive anchoring
19 means.

20 The sheet and blades can be made from materials that have sufficient strength
21 and manufacturability to produce blades, such as, glasses, ceramics, rigid polymers,
22 metals and metal alloys. Examples of metals and metal alloys include but are not
23 limited to stainless steel, iron, steel, tin, zinc, copper, platinum, aluminum, germanium,
24 nickel, zirconium, titanium and titanium alloys consisting of nickel, molybdenum and
25 chromium, metals plated with nickel, gold, rhodium, iridium, titanium, platinum, and the
26 like. An example of glasses include a devitrified glass such as "Photoceram" available
27 from Corning in Corning, NY. Examples of rigid polymers include but are not limited to
28 polystyrene, polymethylmethacrylate, polypropylene, polyethylene, "Bakelite", cellulose
29 acetate, ethylcellulose, styrene/acrylonitrile copolymers, styrenetbutadiene
30 copolymers, acrylonitrile/butadiene/styrene (ABS) copolymers, polyvinyl chloride and
31 acrylic acid polymers including polyacrylates and polymethacrylates.

1 Very dense patterns can be created with unit cells wherein a unit cell has a
2 width A and a length B as illustrated in Figure 3. In one embodiment (not shown), the
3 pattern has the following characteristics: a unit cell area of 0.63 mm by 3.8 mm; the
4 lineal length of a cut in a unit cell is approximately equal to 15 mm; and the open skin
5 length per square centimeter is 625 mm.

6 The microblades of the present invention make an elongated, thin microcut (i.e.,
7 a slit) in the skin surface because the blades have a small thickness (relative to their
8 width and length) resulting in a minimal blade cross-sectional area for the portions of
9 the blade in the skin. The geometry of the microblades 4 results in minimal blade
10 volume in the skin with maximal blade surface area in the skin. The advantages of the
11 present invention include, but are not limited to: (1) the thin blade geometry produces
12 the maximum drug percolation area for a given cross-section of the blade; (2) minimal
13 tissue damage occurs because the amount of blade material in the skin and hence the
14 volume loading is minimized; (3) slanted leading edges (or equivalent pointed shapes)
15 further minimize the amount of volume loading or tissue damage while preserving a
16 large percolation area; (4) for a given volume loading, the larger the surface area, the
17 larger the frictional retaining force in the skin; and (5) for a given desired percolation
18 area, there are fewer blades necessary and therefore the force on each tip is higher
19 making skin penetration easier.

20 In other embodiments (Figures 10-16) other anchoring elements are used in the
21 present invention. In the embodiments shown in Figures 10-14, prong 68 is etched in
22 the side of some or all of the blades 4, and punched lightly so as to protrude outward
23 from the plane of each of the blades, as illustrated in Figures 10 and 14. After the
24 punching of the prongs, the blades may be repunched to regain their substantially
25 vertical orientation. Hinges 72 (Figure 13) can be used to control the retention force of
26 the barb for anchoring. The hinges allow for the retention force to be tailored
27 independently of the size of the blade because the force required to bend or punch the
28 prong is set independently of the size of the blades by the shape or size of the hinge. In
29 other words, the force can be tailored by the amount of attachment of the prong to the
30 plate, the greater the attachment, the greater the force.

1 Prongs may protrude from either side of the blade, or both sides, if desired. The
2 shape of each prong can be any of a variety of shapes such as triangular, square, etc.
3 as shown in Figures 11 and 12. In another embodiment, a curved protrusion 70
4 (Figures 15 and 16) is made by etching a slit in some or all of the blades followed by
5 punching. The prongs and curved protrusions act to anchor the device in the skin
6 similar to the manner described previously.

7 In other embodiments other anchoring elements are used. In the embodiments
8 of Figures 17-19, the blade 4 has additional openings 74 extending through the blade
9 to enhance anchoring. The edges forming the holes or other linear openings are
10 etched through the blade. Alternatively, or in addition, numerous small pits (i.e.,
11 indentations) rather than holes can be etched in the surface of the blade. As described
12 above, the elastic nature of the skin tissue causes the skin to move into the openings or
13 pits. In the embodiments with openings, the skin tissue may heal and reconnect
14 through the openings to provide even greater anchoring.

15 In a further embodiment (Figure 20), a plurality of blades in an opening 8 are
16 arranged at 90° to another plurality of blades in an opening 8' such that anchoring in
17 two directions is obtained. In other words, the blades (not shown) associated with the
18 openings 8 are oriented parallel to the edge 76 of the device 2 and the blades (not
19 shown) associated with the openings 8' are oriented parallel to the edge 78 of the
20 device. The blades associated with each opening 8 can be oriented at any angle with
21 respect to the blades associated with each opening 8'. Alternatively, the blades within
22 each opening can be along perpendicular sides of the openings. In a similar manner,
23 the blades within each opening can be formed in a serrated pattern as illustrated in
24 Figure 21. This pattern allows the blades to have different, controllable angles with
25 respect to each other defined by the angle of the punch used and the etched angle β of
26 the pattern.

27 The number of blades and openings of any of the embodiments of the device 2
28 is variable with respect to the desired flux rate, agent being sampled or delivered,
29 delivery or sampling device used (i.e., electrotransport, passive, osmotic,
30 pressure-driven, etc.), and other factors as will be evident to one of ordinary skill in the
31 art. In general, the larger the number of blades per unit area (i.e., the blade density),

1 the more distributed is the flux of the agent through the skin because there are a
2 greater number of agent-conveying pathways through the skin. Consequently, the
3 smaller the number of blades per unit area, the more concentrated is the flux of the
4 agent through the skin because there are fewer pathways. The present invention has a
5 blade density of at least about 10 blades/cm² and less than about 1000 blades/cm²,
6 preferably at least about 600 blades/cm², more preferably at least about 800
7 blades/cm². In similar fashion, the number of openings per unit area through which the
8 agent passes is at least about 10 openings/cm² and less than about 1000
9 openings/cm². In one embodiment, the present invention produces a percolation area
10 of about 0.005 to .05 cm²/cm² of body surface, preferably about 0.01 cm²/cm² of body
11 surface.

12 One embodiment of the present invention relies on the application of an electric
13 current across the body surface or "electrotransport". Electrotransport refers generally
14 to the passage of a beneficial agent, e.g., a drug or drug precursor, through a body
15 surface such as skin, mucous membranes, nails, and the like. The transport of the
16 agent is induced or enhanced by the application of an electrical potential, which results
17 in the application of electric current, which delivers or enhances delivery of the agent
18 or, for "reverse" electrotransport, samples or enhances sampling of the agent. The
19 electrotransport of the agents into the human body may be attained in various manners.
20 One widely used electrotransport process, iontophoresis, involves the electrically
21 induced transport of charged ions. Electroosmosis, another type of electrotransport
22 process involved in the transdermal transport of uncharged or neutrally charged
23 molecules (e.g. transdermal sampling of glucose), involves the movement of a solvent
24 with the agent through a membrane under the influence of an electric field.
25 Electroporation, still another type of electrotransport, involves the passage of an agent
26 through pores formed by applying an electrical pulse, a high voltage pulse, to a
27 membrane. In many instances, more than one of these processes may be occurring
28 simultaneously to different extents. Accordingly, the term "electrotransport" is given
29 herein its broadest possible interpretation, to include the electrically induced or
30 enhanced transport of at least one charged or uncharged agent, or mixtures thereof,

1 regardless of the specific mechanism(s) by which the agent is actually being
2 transported.

3 It will be appreciated by those working in the field that the present invention can
4 be used in conjunction with a wide variety of electrotransport drug delivery systems, as
5 the invention is not limited in any way in this regard. For examples of electrotransport
6 drug delivery systems, reference may be had to U.S. Patent Nos. 5,147,296 to
7 Theeuwes et al., 5,080,646 to Theeuwes et al., 5,169,382 to Theeuwes et al., and
8 5,169,383 to Gyory et al.

9 Electrotransport devices generally use at least two electrodes which are in
10 electrical contact with some portion of the skin, nails, mucous membranes, or other
11 body surface. In the case of transdermal agent delivery, one of the two electrodes is
12 commonly referred to as the "donor" or "active" electrode, and is the one from which the
13 agent is delivered into the body. In the case of transdermal agent sampling, one of the
14 two electrodes is referred to as the "receptor" electrode, and is the one into which the
15 agent (e.g., body electrolyte) is collected upon being withdrawn from the body. The
16 second electrode is, typically termed the "counter" or "return" electrode, and serves to
17 close the electrical circuit through the body. For example, when the agent to be
18 delivered is a cation, i.e., a positively charged ion, the anode becomes the active or
19 donor electrode, while the cathode serves to complete the circuit. Alternatively, if the
20 agent to be delivered is an anion, i.e., a negatively charged ion, the cathode is the
21 donor electrode. When the agent to be sampled is a cation, the cathode becomes the
22 receptor electrode while the anode serves to complete the circuit. When the agent to
23 be sampled is an anion, the anode becomes the receptor electrode while the cathode
24 serves to complete the circuit. When the agent to be sampled has no net charge (e.g.,
25 glucose), then either the anode, or the cathode, or both electrodes, can serve as the
26 receptor electrode. Both the anode and cathode may be donor electrodes if both
27 anionic and cationic agents are delivered simultaneously. Electrotransport delivery
28 systems generally require at least one reservoir or source of the agent to be delivered
29 to the body. Electrotransport sampling systems likewise require at least one reservoir
30 in which to collect the agent being sampled. Examples of such reservoirs include a
31 pouch or cavity as described in U.S. Patent No. 4,250,878 to Jacobsen et al., a porous

1 sponge or pad as described in U.S. Patent No. 4,141,359 to Jacobsen et al., and a
2 pre-formed gel body as described in U.S. Patent No. 4,383,529 to Webster, among
3 others. Such reservoirs are electrically connected to, and positioned between, the
4 anode or the cathode and the body surface, e.g., to provide a fixed or renewable
5 source of one or more drugs in the case of agent delivery. In addition, electrotransport
6 systems also typically have an electrical power source, e.g., one or more batteries, and
7 an electrical controller designed to regulate the timing, amplitude and/or frequency of
8 the applied electric current, and hence regulate the timing and rate of agent
9 delivery/sampling. This power source component is electrically connected to the two
10 electrodes. Optional electrotransport device components include a counter reservoir,
11 adhesive coatings, insulating separation layers, and rate-controlling membranes.

12 Figures 1 and 22-25 illustrate a representative electrotransport
13 delivery/sampling device 10 that may be used in conjunction with the present invention.
14 Device 10 comprises an upper housing 16, a circuit board assembly 18, a lower
15 housing 20, anode electrode 22, cathode electrode 24, anode reservoir 26, cathode
16 reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral wings 15
17 which assist in holding device 10 on a patient's skin. Printed circuit board assembly 18
18 comprises an integrated circuit 19 coupled to discrete components 40 and battery 32.
19 Circuit board assembly 18 is attached to housing 16 by posts (not shown in Figure 1)
20 passing through openings 13a and 13b, the ends of the posts being heated/melted in
21 order to heat stake the circuit board assembly 18 to the housing 16. Lower housing 20
22 is attached to the upper housing 16 by means of adhesive layer 30, the upper surface
23 34 of adhesive layer 30 being adhered to both lower housing 20 and upper housing 16
24 including the bottom surfaces of wings 15. Shown (partially) on the underside of circuit
25 board assembly 18 is a button cell battery 32. Other types of batteries may also be
26 employed to power device 10 depending on the need.

27 The device 10 is generally comprised of battery 32, electronic circuitry 19,40,
28 electrodes 22,24, drug/receptor reservoir 26, counter reservoir 28, and device 2, all of
29 which are integrated into a self-contained unit. The outputs (not shown in Figure 1) of
30 the circuit board assembly 18 make electrical contact with the electrodes 24 and 22
31 through openings 23,23' in the depressions 25,25' formed in lower housing 20, by

1 means of electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn,
2 are in direct mechanical and electrical contact with the top sides 44',44 of drug
3 reservoirs 26 and 28. The bottom side 46 of drug reservoir 28 contacts the patient's
4 skin through the opening 29 in adhesive layer 30. The bottom side 46' of drug reservoir
5 26 contacts the patient's skin through the plurality of openings 8 in the device 2. The
6 formulation of reservoir 26 is preferably a viscous gel that fills the openings 8 such that
7 the reservoir 26 is in direct contact with the skin when the blades have penetrated the
8 stratum corneum. The contact between the reservoir and skin provides a path for the
9 agent to be transported along. If the reservoir 26 is not in direct contact with the skin
10 initially typically sweat accumulates in the confined area and provides an agent-
11 transmitting pathway between reservoir 26 and the skin.

12 Device 10 optionally has a feature which allows the patient to self-administer
13 a dose of drug, or self-sample a body electrolyte, by electrotransport. Upon
14 depression of push button switch 12, the electronic circuitry on circuit board assembly
15 18 delivers a predetermined DC current to the electrode/reservoirs 22,26 and 24,28 for
16 an interval of predetermined length. The push button switch 12 is conveniently located
17 on the top side of device 10 and is easily actuated through clothing. A double press of
18 the push button switch 12 within a short time period, e.g., three seconds, is preferably
19 used to activate the device, thereby minimizing the likelihood of inadvertent actuation of
20 the device 10. Preferably, the device transmits to the user a visual and/or audible
21 confirmation of the onset of operation by means of LED 14 becoming lit and/or an
22 audible sound signal from, e.g., a "beeper". Agent is delivered/sampled through the
23 patient's skin, e.g., on the arm, by electrotransport over the predetermined interval.
24 Anodic electrode 22 is preferably comprised of silver and cathodic electrode 24 is
25 preferably comprised of silver chloride. Both reservoirs 26 and 28 are preferably
26 comprised of polymeric gel materials. Electrodes 22,24 and reservoirs 26,28 are
27 retained by lower housing 20.

28 In the case of therapeutic agent (i.e., drug) delivery, a liquid drug solution or
29 suspension is contained in at least one of the reservoirs 26 and 28. Drug
30 concentrations in the range of approximately 1×10^{-4} M to 1.0 M or more can be used,
31 with drug concentrations in the lower portion of the range being preferred.

1 The push button switch 12, the electronic circuitry on circuit board assembly 18
2 and the battery 32 are adhesively "sealed" between upper housing 16 and lower
3 housing 20. Upper housing 16 is preferably composed of rubber or other elastomeric
4 material, e.g., injection moldable ethylene vinyl acetate. Lower housing 20 is preferably
5 composed of a plastic or elastomeric sheet material (e.g., polyethylene) which can be
6 easily molded to form depressions 25,25' and cut to form openings 23,23'. The
7 assembled device 10 is preferably water resistant (i.e., splash proof) and is most
8 preferably waterproof. The system has a low profile that easily conforms to the body,
9 thereby allowing freedom of movement at, and around, the wearing site. The reservoirs
10 26 and 28 are located on the skin-contacting side of the device 10 and are sufficiently
11 separated to prevent accidental electrical shorting during normal handling and use.

12 The device 10 adheres to the patient's body surface (e.g., skin) by means of an
13 adhesive layer 30 (which has upper adhesive side 34 and body contacting adhesive
14 side 36) and the anchoring elements on the device 2 of any of the embodiments
15 discussed above. The adhesive side 36 covers the entire underneath side of the
16 device 10 except where the device 2 and reservoir 28 are located. The adhesive side
17 36 has adhesive properties which assures that the device 10 remains in place on the
18 body during normal user activity, and yet permits reasonable removal after the
19 predetermined (e.g., 24-hour) wear period. Upper adhesive side 34 adheres to lower
20 housing 20 and retains the electrodes and reservoirs within housing depression 25,25'
21 as well as retains device 2 to lower housing 20 and lower housing 20 to upper housing
22 16.

23 In one embodiment of the drug delivery or sampling device there is a bandage
24 cover (not shown) on the device 10 for maintaining the integrity of the device when it is
25 not in use. In use, the bandage cover is stripped from the device before the device is
26 applied to the skin.

27 In other embodiments of the present invention, passive transdermal delivery or
28 sampling devices are used with device 2. Two examples of passive transdermal
29 delivery or sampling devices are illustrated in Figures 26 and 27. In Figure 26, passive
30 transdermal delivery device 88 comprises a reservoir 90 containing agent. Reservoir
31 90 is preferably in the form of a matrix containing the agent dispersed therein.

1 Reservoir 90 is sandwiched between a backing layer 92, which is preferably
2 impermeable to the agent, and a rate-controlling membrane 94. In Figure 26, th
3 reservoir 90 is formed of a material, such as a rubbery polymer, that is sufficiently
4 viscous to maintain its shape. If a lower viscosity material is used for reservoir 90, such
5 as an aqueous gel, backing layer 92 and rate-controlling membrane 94 would b
6 sealed together about their periphery to prevent leakage. In a sampling configuration,
7 the reservoir 90 would initially not contain the agent. Located below membrane 94 is
8 microblade array device 2. The device 88 adheres to a body surface by means of
9 contact adhesive layer 96 around the periphery of the device 2 and by the anchoring
10 elements of any of the embodiments described previously. The adhesive layer 96 may
11 optionally contain agent. A strippable release liner (not shown) is normally provided
12 along the exposed surface of adhesive layer 96 and is removed prior to application of
13 device 10 to the body surface.

14 Alternatively, as shown in Figure 27, transdermal therapeutic device 98 may be
15 attached to a body surface by means of a flexible adhesive overlay 100 and the
16 anchoring elements used in device 2. Device 98 is comprised of an agent-containing
17 reservoir 90 (for a delivery configuration) which is preferably in the form of a matrix
18 containing the agent dispersed therein. In a sampling configuration, the reservoir 90
19 would initially not contain the agent. An impermeable backing layer 102 is provided
20 adjacent one surface of reservoir 90. Adhesive overlay 100 maintains the device 98 on
21 the body surface in combination with the anchoring elements of any of the
22 embodiments previously described for device 2. Adhesive overlay 100 can be
23 fabricated together with, or provided separately from, the remaining elements of the
24 device 98. With certain formulations, the adhesive overlay 100 may be preferable to
25 the contact adhesive 96 shown in Figure 26. This is true, for example, where the agent
26 reservoir contains a material (such as, for example, an oily surfactant permeation
27 enhancer) which adversely affects the adhesive properties of the contact adhesive
28 layer 96. Impermeable backing layer 102 is preferably slightly larger than reservoir 90,
29 and in this manner prevents the agents in reservoir 90 from adversely interacting with
30 the adhesive in overlay 100. Optionally, a rate-controlling membrane (not shown in
31 Figure 27) similar to membrane 94 in device 88 (Figure 26) can be provided on the

1 skin/mucosa side of reservoir 90. A strippable release liner (not shown) is also
2 normally provided with device 98 and is removed just prior to application of device 98 to
3 the body surface.

4 The formulation for the passive transdermal devices may be aqueous or non-
5 aqueous based. The formulation is designed to deliver the drug at the necessary
6 fluxes. Aqueous formulations typically comprise water and about 1 to 2 weight percent
7 of a hydrophilic polymer as a gelling agent, such as hydroxyethylcellulose or
8 hydroxypropylcellulose. Typical non-aqueous gels are comprised of silicone fluid or
9 mineral oil. Mineral oil-based gels also typically contain 1 to 2 weight percent of a
10 gelling agent such as colloidal silicon dioxide.

11 The reservoir matrix should be compatible with the delivered agent, any
12 excipients (e.g., flux enhancers, irritation preventing agents) and/or any carrier
13 therefore. When using an aqueous-based system, the reservoir matrix is preferably a
14 hydrophilic polymer, e.g., a hydrogel. When using a non-aqueous-based system, the
15 reservoir matrix is preferably composed of a hydrophobic polymer. Suitable polymeric
16 matrices are well known in the transdermal drug delivery art.

17 When a constant drug delivery rate is desired, the drug is present in the matrix
18 or carrier at a concentration in excess of saturation, the amount of excess being a
19 function of the desired length of the drug delivery period of the system. The drug may,
20 however, be present at a level below saturation without departing from this invention.

21 In addition to the drug, the matrix or carrier may also contain dyes, pigments,
22 inert fillers, permeation enhancers, excipients and other conventional components of
23 pharmaceutical products or transdermal devices known in the art.

24 The amount of drug present in the reservoir and the size of the reservoir is
25 generally non-limited and is an amount equal to or larger than the amount of drug that,
26 in its released form, is effective in bringing about the drugs physiological or
27 pharmacological local or systemic effects.

28 The preferred form in which an agent is delivered or sampled generally
29 determines the type of delivery or sampling system to be used, and vice versa. That is,
30 the selection of a "passive" system which delivers or samples the agent by diffusion or
31 an electrically powered system which delivers or samples the agent by electrotransport

1 will be mostly determined by the form of the agent. For example, with passive delivery
2 systems, it has generally been recognized that the agent is preferably delivered in
3 either its free base or acid form, rather than in the form of a water soluble salt. On the
4 other hand, with electrotransport delivery devices, it has been recognized that the
5 drugs should preferably be ionized and the drug salt should be soluble in water. It is
6 generally believed that the pathways for passive and electrotransported transdermal
7 drug delivery through intact skin are different, with passive delivery occurring through
8 lipid regions (i.e., hydrophobic regions) of the skin and electrotransport delivery
9 occurring through hydrophilic pathways or pores such as those associated with hair
10 follicles and sweat glands. For the case of pierced skin, there is substantial passive
11 flux through the microslits created by the microblades piercing the stratum corneum.
12 The drug for passive delivery is generally hydrophobic, e.g., free base form, whereas
13 the preferred form of a drug for electrotransport delivery is hydrophilic, e.g., water
14 soluble salt form. For osmotic and pressure driven systems which deliver or sample
15 drugs by connective flow carried by a solvent, the drug preferably has sufficient
16 solubility in the carrier solvent. It will be appreciated by those working in the field that
17 the present invention can be used in conjunction with a wide variety of osmotic delivery
18 or sampling systems, as the invention is not limited to a particular device in this regard.
19 Osmotic devices, available for use with the present invention, are disclosed for
20 example in U.S. Patent Nos. 4,340,480 to Eckenhoff, 4,655,766 to Theeuwes et al.,
21 and 4,753,651 to Eckenhoff.

22 This invention has utility in connection with the delivery of drugs within any of
23 the broad class of drugs normally delivered through body surfaces and membranes,
24 including skin. In general, this includes drugs in all of the major therapeutic areas
25 including, but not limited to, anti-infectives such as antibiotics and antiviral agents,
26 analgesics including fentanyl, sufentanil, buprenorphine and analgesic combinations,
27 anesthetics, anorexics, antiarthritics, antiasthmatic agents such as terbutaline,
28 anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines,
29 anti-inflammatory agents, antimigraine preparations, anti-motion sickness preparations
30 such as scopolamine and ondansetron, anti-nauseants, antineoplastics,
31 antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics,

1 including gastrointestinal and urinary anticholinergics, sympathomimetics, xanthine
2 derivatives, cardiovascular preparations including calcium channel blockers such as
3 nifedipine, betablockers, beta-agonists such as dobutamine and ritodrine,
4 antiarrhythmics, antihypertensives such as atenolol, ACE inhibitors such as ranitidine,
5 diuretics, vasodilators, including general, coronary, peripheral and cerebral, central
6 nervous system stimulants, cough and cold preparations, decongestants, diagnostics,
7 hormones such as parathyroid hormone, bisphosphonates, hypnotics,
8 immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics,
9 prostaglandins, psychostimulants, sedatives and tranquilizers. The invention is also
10 useful in conjunction with reducing or preventing sensitization occurring as a result of
11 electrotransport delivery of proteins, peptides and fragments thereof, whether naturally
12 occurring, chemically synthesized or recombinantly produced. The invention may
13 additionally be used in conjunction with the delivery of nucleotidic drugs, including
14 oligonucleotide drugs, polynucleotide drugs, and genes.

15 The present invention has particular utility in the delivery of peptides,
16 polypeptides, proteins, nucleotidic drugs, and other such species through body
17 surfaces such as skin. These substances typically have a molecular weight of at least
18 about 300 daltons, and more typically have a molecular weight of at least about 300 to
19 40,000 daltons. Specific examples of peptides and proteins in this size range include,
20 without limitation, LHRH, LHRH analogs such as goserelin, buserelin, gonadorelin,
21 napharelin and leuprolide, GHRH, GHRF, insulin, insulintropin, calcitonin, octreotide,
22 endorphin, TRH, NT-36 (chemical name:
23 N-[[[(s)-4-oxo-2-azetidiny]carbonyl]-L-histidyl-L-prolinamide), liprecin, pituitary
24 hormones (e.g., HGH, HMG, desmopressin acetate, etc.), follicle luteoids, α ANF,
25 growth factors such as growth factor releasing factor (GFRF), β MSH, GH, somatostatin,
26 bradykinin, somatotropin, platelet-derived growth factor, asparaginase, bleomycin
27 sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin (ACTH),
28 erythropoietin, epoprostenol (platelet aggregation inhibitor), glucagon, HCG, hirulog,
29 hyaluronidase, interferon, interleukins, menotropins (urofollitropin (FSH) and LH),
30 oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin,
31 desmopressin, ACTH analogs, ANP, ANP clearance inhibitors, angiotensin II

1 antagonists, antidiuretic hormone agonists, bradykinin antagonists, ceredase, CSI's,
2 calcitonin gene related peptide (CGRP), enkephalins, FAB fragments, IgE peptide
3 suppressors, IGF-1, neurotrophic factors, colony stimulating factors, parathyroid
4 hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists,
5 pentigetide, protein C, protein S, renin inhibitors, thymosin alpha-1, thrombolytics, TNF,
6 vaccines, vasopressin antagonists analogs, alpha-1 antitrypsin (recombinant), and
7 TGF-beta.

8 As mentioned above, the device 2 of the present invention can also be used
9 with known sampling devices including, but not limited to, reverse iontophoresis,
10 osmosis, passive diffusion, phonophoresis, and suction (i.e., negative pressure).
11 Figure 28 illustrates an osmotic sampling device 104 in combination with any of the
12 embodiments described previously for device 2. Osmotic sampling devices can be
13 used to sample any of a variety of agents (e.g., body analytes, licit and illicit drugs)
14 through a body surface including, but not limited to glucose, body electrolytes, alcohol,
15 blood gases, and illicit substances such as drugs of abuse. The osmotic sampling
16 device 104 is attached to a body surface by means of a flexible adhesive overlay 100
17 and the anchoring elements of device 2. Device 104 is comprised of a salt layer 106
18 located between a semi-permeable or osmotic membrane 94 and an optional agent
19 sensing element 108. The optional agent sensing element can be any of a variety of
20 chemically reactive sensors and indicators, for example the color indicating test strips
21 associated with glucose testing. The adhesive overlay 100 can have a cut-out or
22 transparent window in the area of the indicators so that the indicators can be readily
23 viewed. In an alternate embodiment, the agent sensing element can be located
24 between the device 2 and the salt layer.

25 The following example is merely illustrative of the present invention and should
26 not be considered as limiting the scope of the invention in any way, as this example
27 and other equivalents thereof will become apparent to those versed in the art and in
28 light of the present disclosure, drawings, and the accompanying claims.

Example

The effect of the present design was evaluated on the skin resistance of a hairless guinea pig. A blade array of two square centimeters was applied to ECG electrodes of five square centimeters. The blade array and electrodes were then applied to the skin of the animal. Resistance measurements were taken two minutes after application of the electrode to the skin of the animal. A decrease in resistance was observed indicating that penetration of the blades into the skin had occurred.

The device was evaluated for its effect on electrotransport flux of a decapeptide in the hairless guinea pig. The following are specifications for the device: the device consisted of a sheet having a plurality of rectangular openings having six blades, three on each long side of a 860 μm by 250 μm rectangle resulting in a 0.22 mm^2 open area for each opening. Each set of three blades started at the opposite end of the rectangle as the opposing set of blades. All of the blades were about 200 μm long. All six blades had slanted leading edges and the blade at each end was barbed as well. The group of six blades were arranged in two slightly offset rows with ten groups in each row on the sheet. Each device was a two cm^2 piece of stainless steel 25 μm thick etched and punched with eight pairs of offset rows or 160 groups of six blades for a total of 960 blades. There were 40 void areas per cm^2 and 240 blades per cm^2 .

For the study, a one compartment electrotransport system was used. It consisted of a cathode compartment containing a Dulbecco's phosphate buffered saline imbibing gel and a donor anode compartment containing two millimoles of decapeptide buffered at pH 7.5, 10% cholestyramine chloride and 3% hydroxyethylcellulose. After loading the gels in the system, the release liner was removed from the adhesive foam bottom of the electrotransport system. The device was carefully applied over a 1.6 cm diameter hole containing the donor gel with the microblades facing away from the gel. The electrotransport system was then placed on the skin of a lightly anesthetized hairless guinea pig. The systems were applied to the backs of the animals using gentle downward pressure while at the same time pushing bottom side of the system with the thumb of the technician. (The thumb trapped a roll of the animals' skin which allowed some upward pressure to be applied directly to the bottom side of the skin in contact

1 with the device microblades). After two minutes the current and resistance
2 measurements were observed and recorded. The electrotransport system was
3 wrapped with Vetrap and the animals were returned to their cages for the duration of
4 electrotransport (5 and 24 hours). Decapeptide flux was evaluated by measuring
5 urinary excretion of this peptide. Only a modest effect of the device on decapeptide
6 flux was observed in the first five hours of transport. Between five and twenty-four
7 hours, the electrotransport flux of an ordinary electrotransport device dropped very
8 significantly probably due to collapse of the pathways or possibly aggregation of the
9 peptide in the pathways (the decrease in flux between five and twenty-four hours was
10 reproducible). Use of the blade array device completely prevented this decrease in flux
11 and resulted in an overall ten-fold increase in decapeptide flux over a twenty-four hour
12 transport period.

13 While the invention has been described in conjunction with the preferred
14 specific embodiments thereof, it is to be understood that the foregoing description as
15 well as the example are intended to illustrate and not limit the scope of the invention.
16 Other aspects, advantages and modifications within the scope of the invention will be
17 apparent to those skilled in the art to which the invention pertains.

1 **WHAT IS CLAIMED IS:**

2

3 1. A device (2) for piercing the stratum corneum of a body surface to form
4 pathways through which an agent can be introduced or withdrawn, comprising:

5 a sheet (6) having at least one opening (8) therethrough and a plurality of
6 blades (4) extending downward therefrom, at least one of the plurality of blades having
7 an anchor (50,68,74,82) for anchoring the device (2) to the body surface.

8 2. A device (2) for piercing the stratum corneum of a body surface to form
9 pathways through which an agent can be introduced or withdrawn, comprising:

10 a sheet (6) having at a plurality of openings (8) therethrough, at least one of said
11 openings (8) having a plurality of blades (4) located along a periphery thereof and
12 extending downward from the sheet (6), and an anchor (50,68,74,82) for anchoring the
13 device (2) to the body surface.

14 3. The device of Claim 1 or 2, wherein the anchor is selected from the group
15 consisting of:

16 (i) a projection (68) extending out from at least one blade (4);

17 (ii) a barb (50);

18 (iii) at least one opening (74) extending through at least one blade (4);

19 (iv) an adhesive on a body contacting surface (48) of the sheet (6) and on at
20 least one surface (82) of at least one of the plurality of blades (4);

21 (v) each of the blades (4) having an axis, the blades (4) being oriented
22 so that the blade axes are substantially parallel and the axes form an angle of
23 about 1° to about 89° relative to the sheet (6);

24 (vi) each one of the plurality of blades (4) defines essentially a plane and
25 wherein the anchor comprises a portion of the plurality of blades being oriented at an
26 angle of about 90° with respect to a remaining portion of the plurality of blades; and

27 (vii) each one of the plurality of blades (4) defines essentially a plane and
28 wherein the anchor comprises a portion of the plurality of blades (4) being oriented at
29 an angle within a range of about 1° to about 89° with respect to a remaining portion of
30 the plurality of blades (4).

- 1 4. The device of Claim 3, wherein the projection (68) extends out from a plane
2 defined by the at least one blade (4).
- 3 5. The device of Claim 4, wherein the projection (68) is a prong (4).
- 4 6. The device of Claim 3, wherein the projection is integral with an edge of the
5 at least one blade and in a plane defined by the at least one blade.
- 6 7. The device of Claim 1 or 2, further comprising a therapeutic agent delivery
7 device (10,88,98,104) connected to the piercing device (2) and positioned to deliver a
8 therapeutic agent through the openings (8) to the body surface, the agent delivery
9 device (10,88,98,104) being selected from the group consisting of an electrotransport
10 device (10), a passive diffusion device (88,98), an osmotic device (104), and a
11 pressure driven device.
- 12 8. The device of Claim 7, wherein the agent comprises a polypeptide or protein.
- 13 9. The device of Claim 1 or 2, further comprising a sampling device
14 (10,88,98,104) connected to the piercing device and positioned to sample a substance
15 from the body surface through the opening(s) (8), the sampling device being selected
16 from the group consisting of a reverse electrotransport device (10), a passive diffusion
17 device (88,98), an osmotic device (104), and a negative pressure driven device.
- 18 10. The device of Claim 9, wherein the sampled substance is selected from the
19 group consisting of body electrolytes, illicit drugs and glucose.
- 20 11. The device of Claim 1, wherein a portion of the plurality of blades (4) are
21 located along a periphery of an opening (8) through the sheet (6).
- 22 12. The device of Claim 1 or 2, further comprising a plurality of second
23 openings (80) through the sheet (6) being spaced between the plurality of openings (8).
- 24 13. The device of Claim 1 or 2, wherein the device has about 600 to about 1000
25 blades/cm².
- 26 14. The device of Claim 1 or 2, wherein the device has at least about 800
27 blades/cm².
- 28 15. The device of Claim 1 or 2, wherein at least a portion of the plurality of
29 blades (4) have a length sufficient to pierce the stratum comeum of the body surface to
30 a depth of at least about 25 μ m.

1 16. The device of Claim 1 or 2, wherein each of the plurality of blades (4) is
2 oriented approximately perpendicular to the sheet (6).

3 17. The device of Claim 1 or 2, wherein each of the plurality of blades (4) is
4 oriented at an angle in the range of about 1° to about 89° to the sheet (6).

5 18. The device of Claim 1 or 2, wherein each of the plurality of blades (4) is
6 oriented at an angle in the range of about 10° to about 60° to the sheet (6).

7 19. The device of Claim 1 or 2, wherein at least a portion of the plurality of
8 blades (4) have a thickness in the range of about 7 µm to about 100 µm.

9 20. The device of Claim 1 or 2, wherein at least a portion of the plurality of
10 blades (4) have a thickness in the range of about 25 µm to about 50 µm.

11 21. The device of Claim 1 or 2, wherein the plurality of blades (4) is composed
12 of a material selected from the group consisting of metals, metal alloys, glasses,
13 ceramics and rigid polymers.

14 22. The device of Claim 1 or 2, wherein the sheet (6) and the plurality of blades
15 (4) are substantially impermeable to the passage of the agent.

16 23. The device of Claim 1 or 2, wherein the plurality of blades (4) are thinner
17 than the sheet (6).

18 24. A method for producing a device (2) for piercing the stratum corneum of a
19 body surface, the method comprising:

20 applying a layer of photo-resist to a first side (49) of a sheet (6);

21 exposing the layer of photo-resist through a mask pattern for producing a
22 plurality of blades (4);

23 etching exposed portions of the photo-resist and the sheet (6) to produce the
24 plurality of blades (4) and openings (8) through the sheet (6);

25 punching the plurality of blades (4) through the openings (8) such that the
26 plurality of blades (4) extend downward from the sheet (6); and

27 incorporating the device (2) for piercing the stratum corneum into a delivery
28 device (10,88,98,104) or sampling device (10,88,98,104).

29 25. The method of Claim 24, wherein the photo-resist is a resist selected
30 from the group consisting of wet resist and dry resist.

31 26. The method of Claim 24 wherein the etching step comprises spray etching.

1 27. The method of Claim 24 wherein the punching step comprises:
2 placing the sheet (6) on a die (52) having a plurality of openings (56)
3 corresponding to the plurality of blades (4) and openings (8) of the sheet (6); and
4 bending the plurality of blades (4) through the openings (56) to be substantially
5 perpendicular to the sheet (6) with a punch (54) having a plurality of protrusions (58)
6 corresponding to the plurality of openings (56) in the die (52) and the plurality of
7 openings (8) of the sheet (6).

8 28. A method of transdermally sampling an agent, comprising:

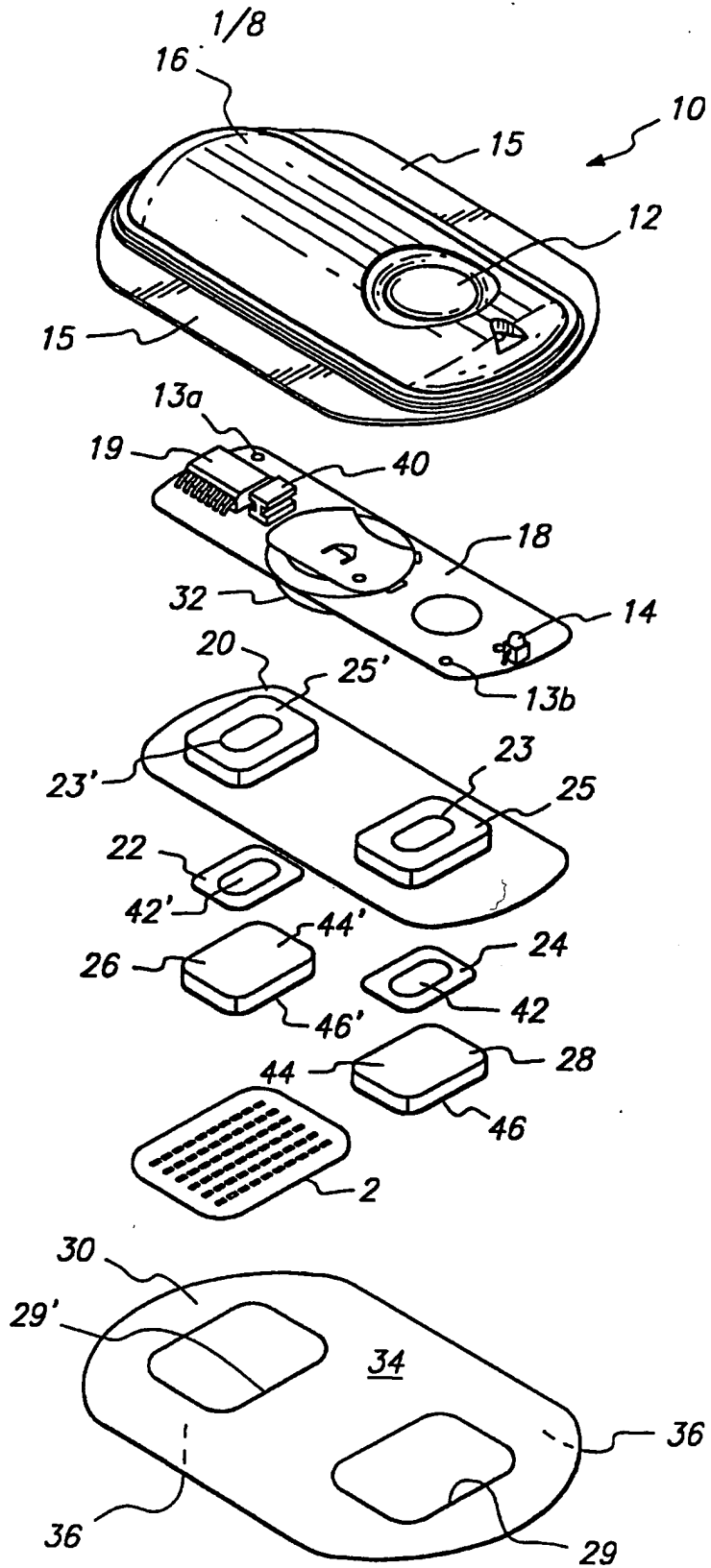
- 9 a. placing a device (2) on a body surface through which the agent is to be
10 withdrawn, the device (2) including a sheet (6) having at least one opening (8)
11 therethrough and a plurality of blades (4) extending downward therefrom whereby
12 agent transmitting pathways are formed through the stratum corneum at the body
13 surface, and a reservoir (26, 90, 106) in agent transmitting relation with the opening (8);
14 b. withdrawing the agent through the pathways and said opening (8); and
15 c. collecting the agent in the reservoir (26,90,106).

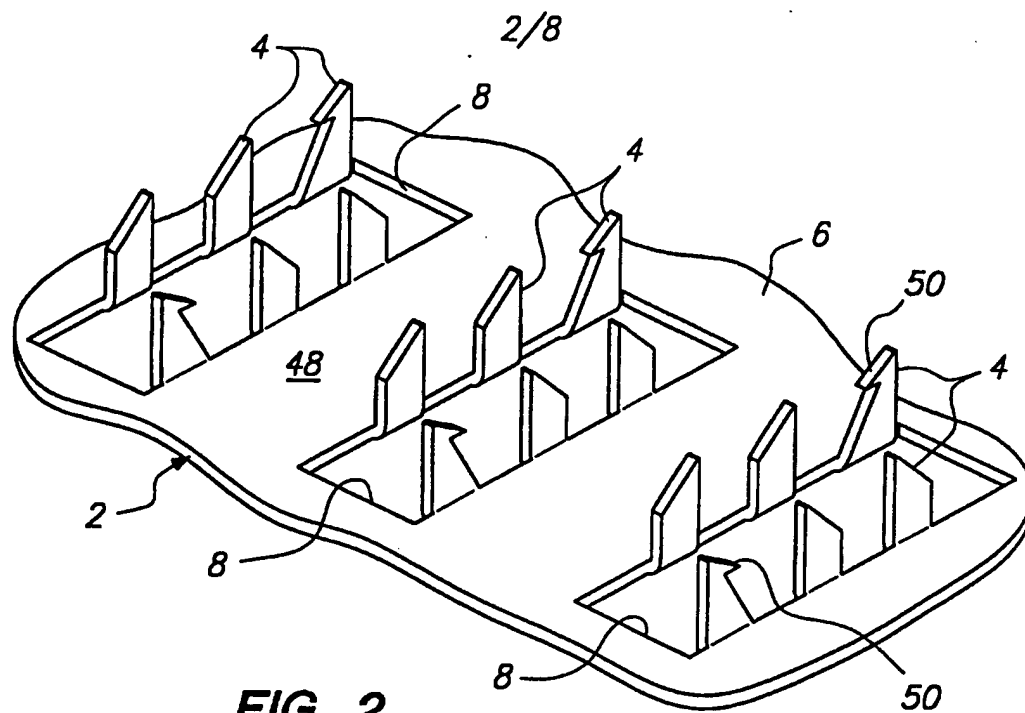
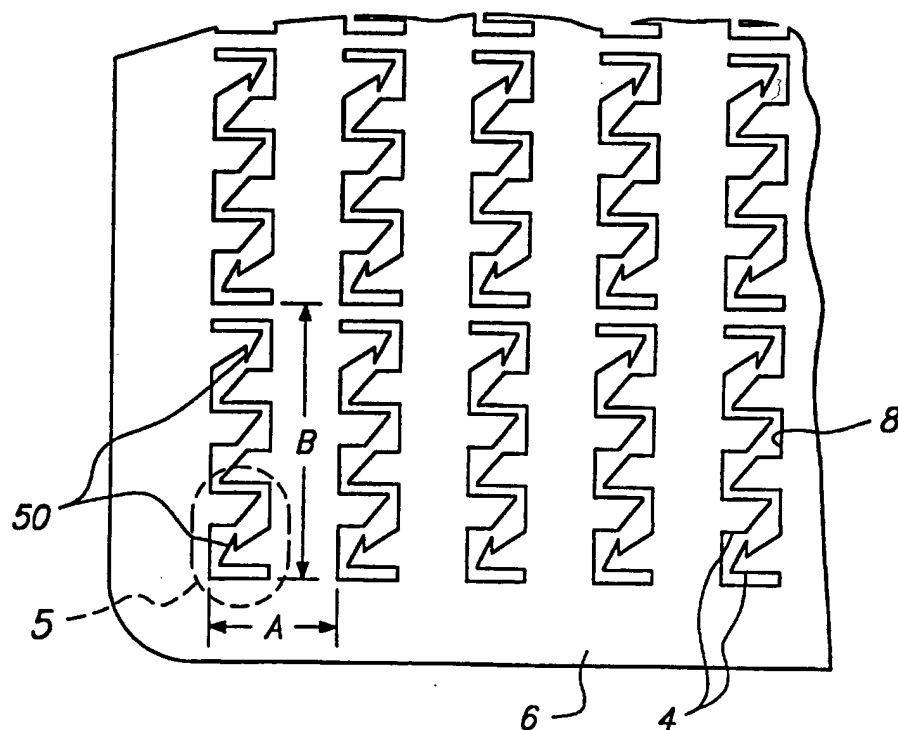
16 29. The method of Claim 28, wherein the sampled agent is selected from the
17 group consisting of body analytes, electrolytes, blood gases, illicit drugs, licit drugs and
18 glucose.

19 30. The method of Claim 28, further comprising:

- 20 connecting a sampling device (10,88,98,104) to a side opposite of a side (48) of
21 the sheet (6) having the blades (4) extending downward therefrom, the sampling device
22 (10,88,98,104) being selected from the group consisting of a reverse electrotransport
23 sampling device (10), a passive sampling device (88,98), an osmotic sampling device
24 (104), and a negative pressure driven sampling device.

FIG. 1



**FIG. 2****FIG. 3**

3/8

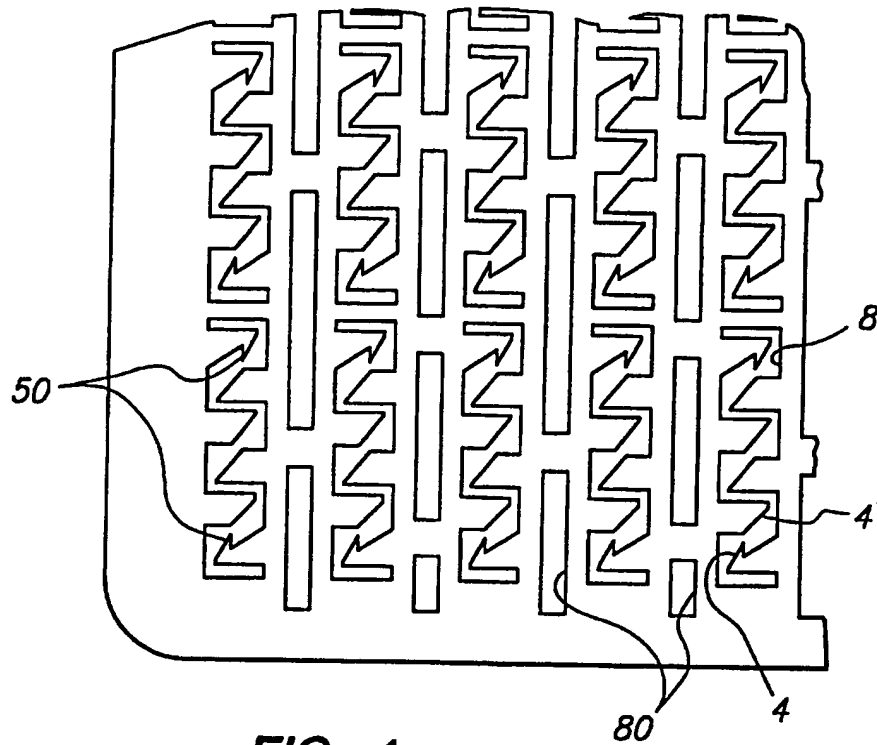


FIG. 4

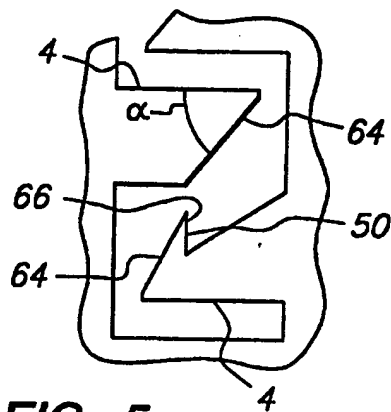


FIG. 5

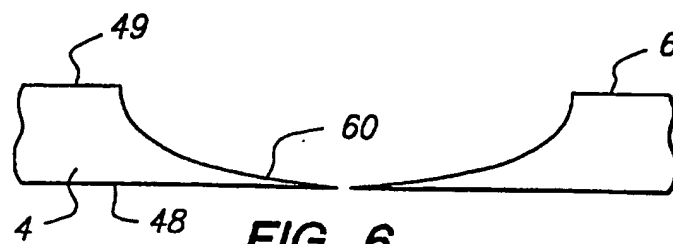
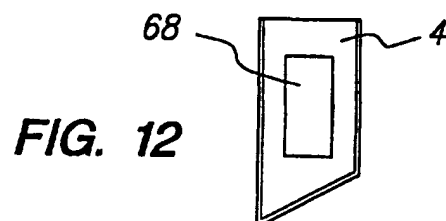
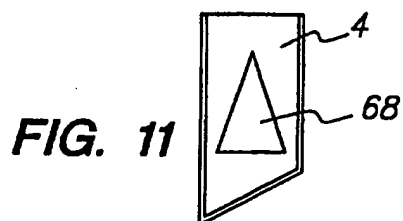
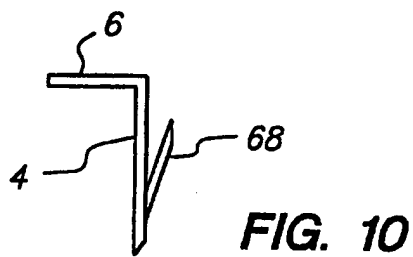
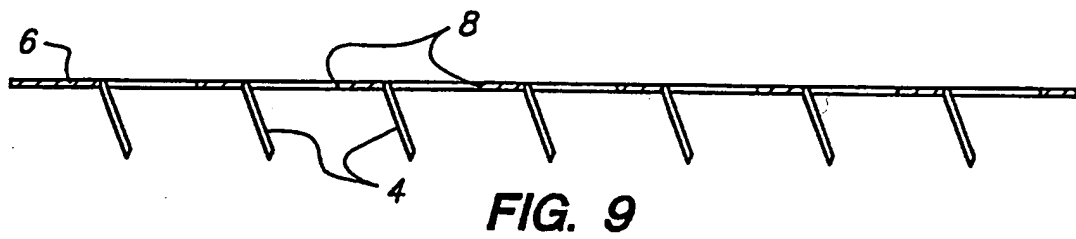
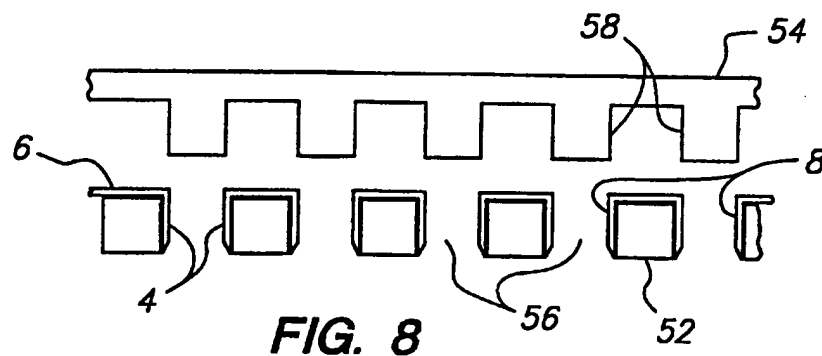
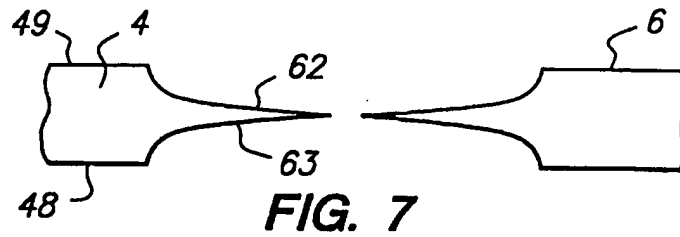


FIG. 6

4/8



5/8

FIG. 13

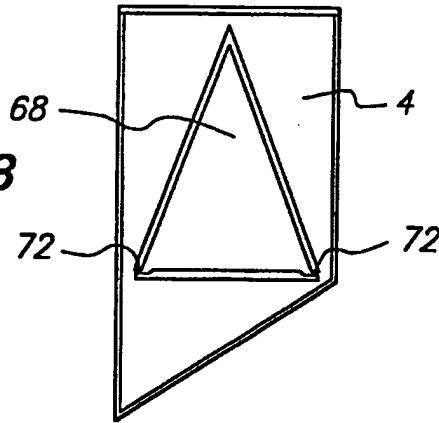


FIG. 14

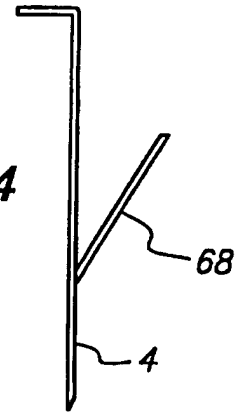


FIG. 15

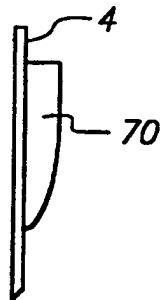


FIG. 16

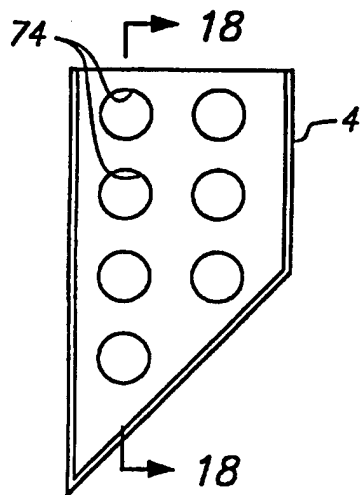
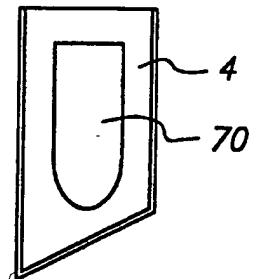


FIG. 17

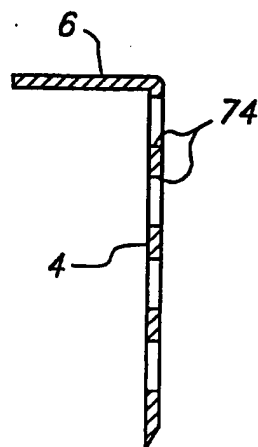


FIG. 18

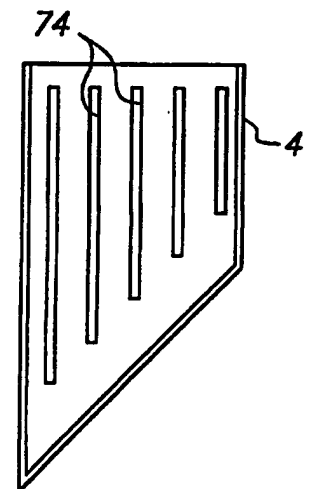


FIG. 19

6/8

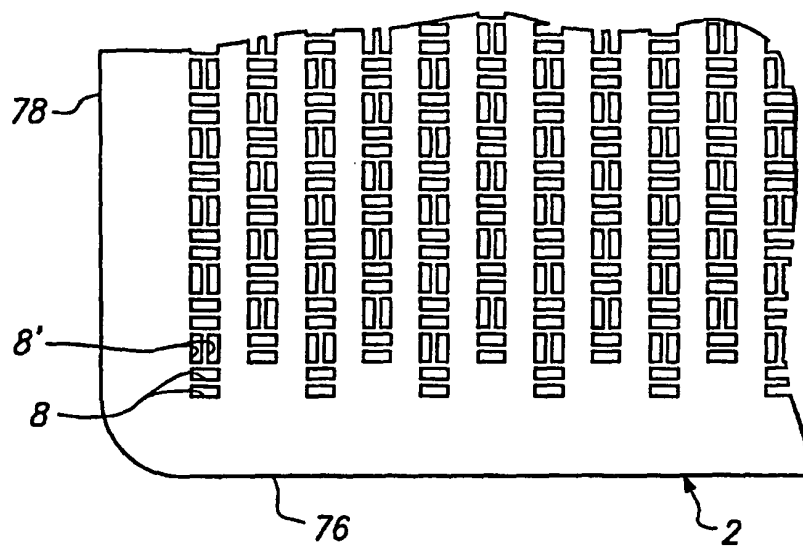


FIG. 20

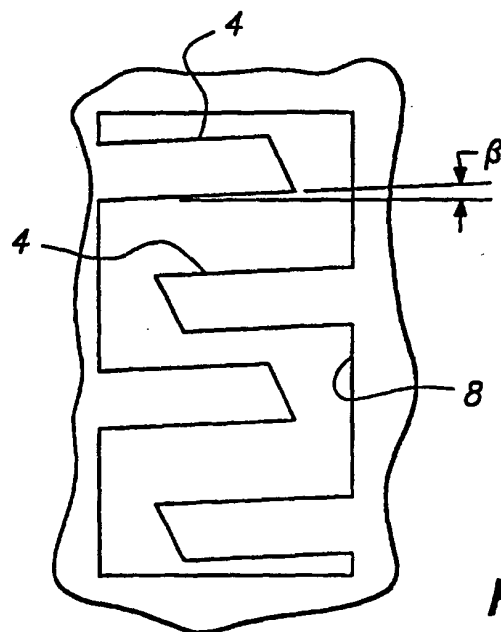


FIG. 21

7/8

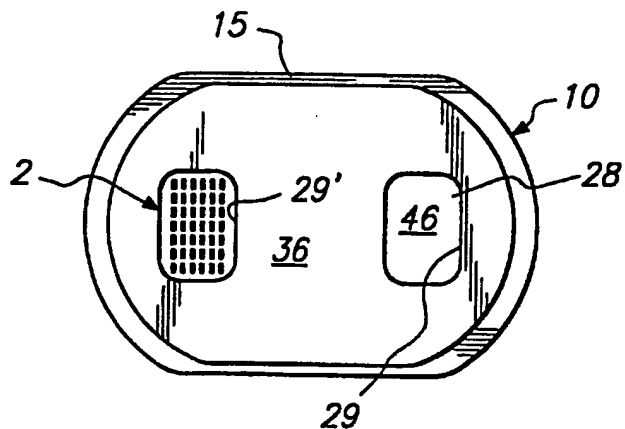


FIG. 22

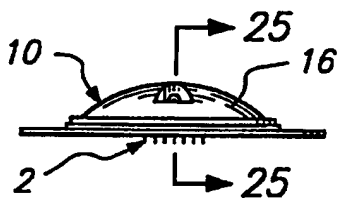


FIG. 23

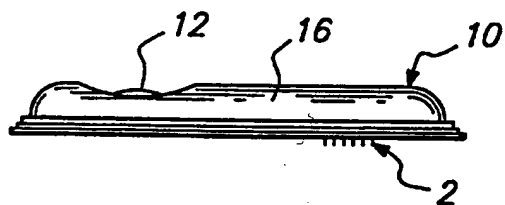


FIG. 24

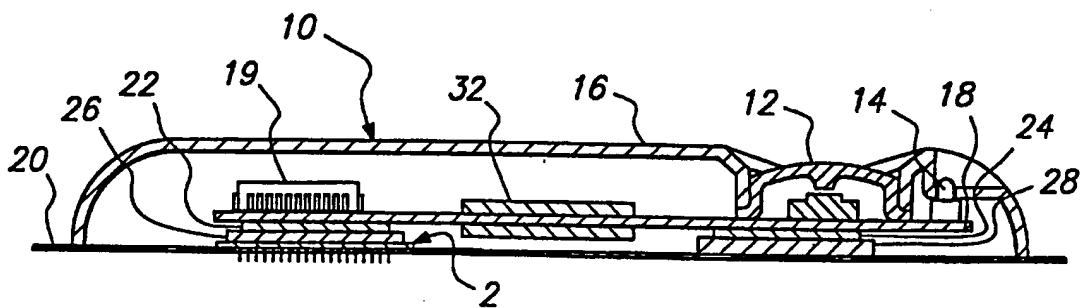


FIG. 25

8/8

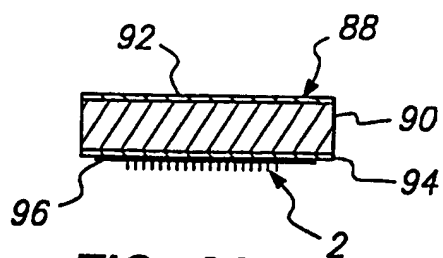


FIG. 26

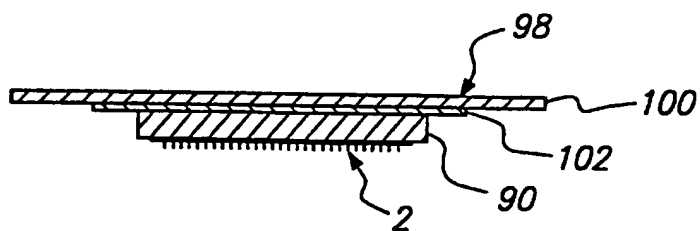


FIG. 27

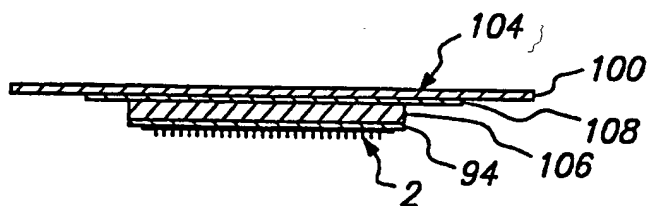


FIG. 28

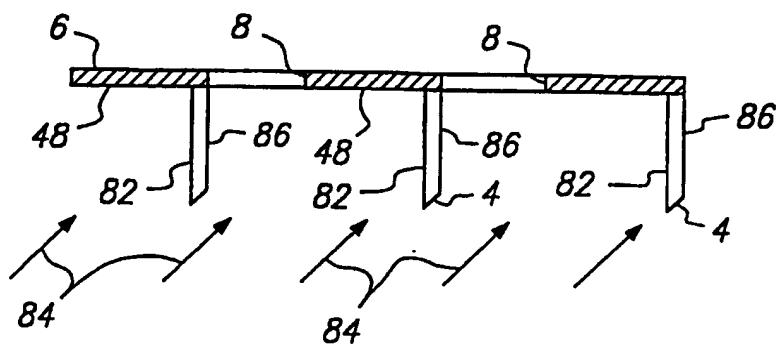


FIG. 29

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/10516

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 17648 A (CIBA GEIGY AG ;EFFENHAUSER CARLO STEFAN (DE); MANZ ANDREAS (CH)) 13 June 1996	1-3,7,8, 11,15-17
Y	see page 7, line 28 - page 12, line 27; figures	28-30
Y	--- US 5 279 543 A (GLIKFELD ET AL.) 18 January 1994	28-30
A	cited in the application see column 3, line 64 - column 4, line 49; figures 7,8	1,9,10
A	--- US 5 279 544 A (GROSS ET AL.) 18 January 1994	1-5,7, 15,16, 21,24
	cited in the application see page 2, line 58 - page 7, line 10; figures	
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

22 October 1997

Date of mailing of the international search report

10.11.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Rakotondrajaona, C

INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/US 97/10516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 964 482 A (GERSTEL MARTIN S ET AL) 22 June 1976 cited in the application see column 4, line 21 - column 7, line 20; figures	1-5,7, 15,16,24

A	US 5 250 023 A (LEE ET AL.) 5 October 1993 cited in the application see column 1, line 29 - column 11, line 8; figures	1-5,7, 15,24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/10516

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9617648 A	13-06-96	AU 4256496 A EP 0796128 A	26-06-96 24-09-97
US 5279543 A	18-01-94	AT 129909 T AU 639888 B AU 3183889 A DE 68924716 D DE 68924716 T DK 179390 A EP 0326398 A EP 0673622 A ES 2085863 T IE 63406 B JP 4502561 T KR 9711449 B PT 89560 B WO 8906989 A US 5362307 A	15-11-95 12-08-93 25-08-89 14-12-95 04-07-96 28-07-90 02-08-89 27-09-95 16-06-96 19-04-95 14-05-92 11-07-97 31-05-95 10-08-89 08-11-94
US 5279544 A	18-01-94	US 5156591 A AT 156375 T DE 69312916 D WO 9317754 A EP 0630276 A JP 7508427 T US 5527288 A AT 142115 T AU 642112 B AU 9058791 A DE 69121881 D DE 69121881 T WO 9210234 A EP 0516783 A JP 5504711 T NZ 240875 A ZA 9301775 A	20-10-92 15-08-97 11-09-97 16-09-93 28-12-94 21-09-95 18-06-96 15-09-96 07-10-93 08-07-92 10-10-96 03-04-97 25-06-92 09-12-92 22-07-93 27-04-94 30-09-93
US 3964482 A	22-06-76	NONE	
US 5250023 A	05-10-93	EP 0429842 A	05-06-91

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/10516

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5250023 A		EP 0509122 A	21-10-92
		JP 1892430 C	26-12-94
		JP 3151982 A	28-06-91
		JP 6014980 B	02-03-94
		CA 2041250 A,C	23-11-91
